REMARKS

Prior to entry of this amendment, claims 80, 81, 90-97 and 100-103 were pending; of these, claims 91-93 were withdrawn from consideration. By this amendment, claims 80, 81, 90 and 100 are amended; and new claims 104-108 are added.

Support for the amendments and new claims can be found throughout the specification. Exemplary support for the amendment of claim 80 to recite "aberrant activity" and for claim 90 to recite "selecting a subject . . ." can be found in the specification at page 32, lines 19-23. Exemplary support for new claim 104 to recite "*in vitro*" can be found at page 13, lines 31-34; exemplary support for new claims 105 and 107 to recite "detecting or monitoring inhibition of angiogenesis" can be found at page 16, lines 10-14; and exemplary support for new claims 106 and 108 to recite "detecting or monitoring reduction in tumor growth" can be found at page 37, lines 4-14. Applicants reserve the right to pursue at a later date any subject matter removed from consideration by this amendment.

No new matter is introduced by the amendments made herein, including the newly-added claims. After entry of this amendment, **claims 80, 81, 90-97, and 100-108 are pending in this application** (of which claims 91-93 are withdrawn).

Office action of January 5, 2011 and *Information Disclosure Statement*

Applicants thank Examiner Pagonakis for vacating the Office action dated January 5, 2011 and replacing it with the current Office action.

Applicants also thank the Examiner for acknowledging that she considered the references cited on the Information Disclosure Statement submitted to the Office on September 10, 2010. The initialed PTO-Form 1449 was attached to the Office action dated January 5, 2011.

Rejections under 35 U.S.C. §102(b)

Claims 80, 81, 90, 94-97 and 100-103 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Japanese Patent No. 10212235 (hereafter JP10212235) as evidenced by the

National Cancer Institute Slide entitled "What is tumor angiogenesis?" (hereinafter the NCI Slide). Applicants traverse this rejection for the following reasons.

JP10212235 does not describe selecting a subject who is expressing GRP aberrantly

The Office asserts that "JP 10212235 clearly states that compounds of formula (I), including the elected compound, are useful for the treatment of tumors" (Office action, at page 5). The MPEP at §2131 states that "to anticipate a claim, [a] reference must teach every element of the claim." Solely to advance prosecution in this application, claims 90 and 100 have been amended to recite a step of "***selecting a subject*** who is expressing GRP aberrantly and is in need of such treatment."

Applicants submit that JP10212235 does not describe selecting a subject for treatment with the particular characteristic of aberrant GRP expression or aberrant GRP activity. In support of Applicants' position that JP10212235 is not an anticipatory reference, submitted herewith is a Declaration under 37 C.F.R. § 1.132 by Dr. Frank Cuttitta (hereafter, the Cuttitta Declaration), who is the first-listed inventor on the subject application. Dr. Cuttitta summarizes JP10212235 as follows:

> JP10212235 describes compounds of generic Compound I as anti-tumor agents. JP10212235 also describes the synthesis and some chemical properties of 131 species of Compound I. As discussed above, ***describing a compound as an "anti-tumor" agent does not indicate any necessary particular biological activity to one of skill in the art. The biological properties of the agent must either be determined from experimental data, implied by particular methods of its use (i.e. monitoring efficacy through measurement of a particular property such as angiogenesis), or knowledge in the art of analogous compounds***. JP10212235 describes an anti-proliferative activity of nine species of Compound I (discussed below), but JP10212235 does not describe any effect of any compound on angiogenesis, nor does JP10212235 suggest that Compound I or any of its species can inhibit angiogenesis. ***Additionally, JP10212235 does not describe any criteria for selecting patients for administration of Compound I and its species (e.g. patients aberrantly expressing GRP, having an aberrant GRP activity, or diagnosed with a cancer type known to express the GRP receptor)***. Nor does JP10212235 describe criteria for measuring or detecting in vivo efficacy of the described compounds other than increased animal survival. For example, JP10212235 does not describe measuring reduction in tumor-induced angiogenesis nor measuring reduction in tumor size. (Emphasis added, *Cuttitta Declaration*, ¶7.1)

Because JP10212235 does not teach the step of selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity, Applicants submit that the reference cannot and does not anticipate amended claims 90 or 94-103.

JP10212235 does not inherently describe inhibiting angiogenesis

The MPEP at §2112 describes the "Requirements for Rejections Based on Inherency." In describing the rationale or evidence necessary to establish inherency, the MPEP states that "the fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (citations omitted).

Applicants submit that the description in JP10212235 is not sufficient to establish inherent anticipation of Applicants' claims under the requirements set forth by the MPEP. The Office concludes that several aspects of the claimed invention are necessarily taught by JP10212235. Applicants respectfully request reconsideration of these conclusions in view of Dr. Cuttitta's Declaration as discussed herein.

<u>An Anti-tumor Treatment Does Not Necessarily Inhibit Angiogenesis</u>

Claims 94-97, 100-103 and 105-108 recite methods of inhibiting angiogenesis mediated growth of a solid tumor. Dr. Cuttitta notes that "JP10212235 does not describe any effect of any compound on angiogenesis, nor does JP10212235 suggest that Compound I or any of its species can inhibit angiogenesis" (*Cuttitta Declaration*, ¶7.1). However, the Office asserts that "treatment of a tumor would necessarily inhibit angiogenesis since angiogenesis is responsible for the progression of the disease" (Office action, at page 4). To support this assertion, the

Office cites the NCI slide. Applicants respectfully disagree with the Office's understanding of tumor progression and those processes that are ***necessarily*** inhibited by treatment of a tumor.

In his Declaration, Dr. Cuttitta states that progression of a tumor requires angiogenesis ***as well as*** cell proliferation, and it is well understood that an anti-tumor treatment can target one or both of these processes. Dr. Cuttitta discusses that one of skill in the art could not and would not assume the target of a given tumor treatment in the absence of experimental evidence and notes that JP10212235 provides no evidence of an anti-angiogenic effect of the described compounds. Dr. Cuttitta contrasts this lack of described angiogenic effect in JP10212235 with the abundant data related to inhibition of angiogenesis in the subject specification (discussed in detail in Dr. Cuttitta's Declaration submitted on September 10, 2010; hereafter the September 2010 Declaration).

> Tumor progression requires two distinct biological processes: (1) cell proliferation and (2) angiogenesis. Cell proliferation requires action of one or more factors on or in a *tumor cell* to induce cell division. Angiogenesis requires action of one or more factors on *endothelial cells* of preexisting blood vessels to induce formation of new blood vessels. To develop beyond a small, size-restricted colony, a tumor requires an adequate blood supply, and must induce angiogenesis. This process, sometimes referred to as the "angiogenic switch," is reviewed in detail by Hanahan and Folkman (*Cell*, 86:353-364, 1996; submitted herewith as **Exhibit BB**).
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> However, even with an abundant blood supply, a tumor *will not expand* and the disease *will not progress* without tumor cell proliferation. Thus, an effective anti-tumor therapy might inhibit proliferation and not affect angiogenesis. Likewise, an effective anti-tumor therapy might target angiogenesis without affecting proliferation. It is possible that a given tumor treatment will inhibit *both* cell proliferation and angiogenesis, but one of skill would not and could not make this conclusion, or any conclusion about the target of a therapy, without explicit experimental evidence. It is common to classify anti-tumor treatments by their mode of function, including effects on proliferation and angiogenesis (*see* for example the table on page 118 of Butowski and Chang, *Cancer Control*, 12:116-124, 2005; submitted herewith as **Exhibit CC**). Thus, without data showing inhibition of angiogenesis (and there is no such data in the cited reference), I could not and would not conclude that the stated "anti-tumor effect" of JP10212235 necessarily inhibits angiogenesis. In contrast, the subject application describes clearly that the recited compound of formula XV' (referred to herein as Compound 77427) inhibits angiogenesis mediated growth of a solid tumor, and this anti-angiogenic effect is explicitly demonstrated. The anti-angiogenic properties of Compound 77427 are described extensively in the subject specification as discussed in the September 2010 Declaration (*see* ¶¶10-12).

The NCI slide does not change the above conclusion about what JP10212235 *necessarily* describes. The NCI slide provides a "birds-eye" schematic view of tumor-induced angiogenesis. The slide illustrates tumor-induced blood vessel formation by release of angiogenesis-stimulating factors into the surrounding normal tissue. The NCI slide only indicates that induction of angiogenesis results in a "tumor that can grow and spread." Implicit in this illustration is the requirement for *proliferation in addition to angiogenesis* for a tumor to grow and spread. Thus, the NCI slide does not indicate that any given anti-tumor treatment will *necessarily* inhibit angiogenesis. (*Cuttitta Declaration*, ¶¶6.1-6.3)

The Data in JP10212235 Does Not Demonstrate Inhibition of Angiogenesis

JP10212235 provides experimental support for an ***anti-proliferative*** effect of some of the described compounds. But neither the *in vitro* nor *in vivo* data necessarily teach an anti-angiogenic effect of the tested compounds and do not imply anything about a general effect of all species of Compound I. Dr. Cuttitta notes that one reason one of skill cannot infer a general effect from the presented data is due to a complete absence of understanding of the mechanism of the described compounds. Dr. Cuttitta contrasts this with the abundant understanding of the mechanism of recited Compound 77427.

Dr. Cuttitta describes the experiments presented in JP10212235 and their reasonable interpretation as follows:

JP10212235 supports its description of Compound I and its species having anti-tumor properties with two sets of experiments. The first (shown in Tables 27-31) presents the *in vitro* effect of nine species (Compound 14, 44, 45, 63, 64, 70, 71, 78, or 125) on *proliferation of 54 different cancer cell lines*. No effect on angiogenesis was tested or implied by these experiments. Tables 27-31 show that many of the listed species have anti-proliferative activity. But each table has at least one blank space where no data is reported for a given species (*see* for example Table 30, Compounds 44, 45, and 63). I conclude that these omissions indicate that no anti-proliferative effect was observed using the given species on the indicated cell line. More generally, these results demonstrate: (1) **considerable variability** among the biological effects of the tested compounds, and (2) the anti-proliferative effect of every species of Compound I **cannot be assumed** for every cancer type listed in JP10212235 or even every cell line tested; it must be experimentally determined.

These conclusions do not contradict my previous statements about the efficacy of Compound 77427 to treat a wide variety of GRP-related conditions (*see* the September 2010 Declaration, ¶14). As discussed therein, Compound 77427 was identified as a small molecule mimetic of the GRP functional antagonist monoclonal antibody 2A11. Thus, one of skill could reasonably predict that Compound 77247 will be useful to treat any disease or condition known to be mediated by aberrant GRP expression. In contrast, the

biological target(s) of Compound I and its species is neither described nor suggested. JP10212235 does not suggest that Compound I and its species share a biological target (*e.g.* a particular protein). Thus, one of skill could not make the same inference about Compound I and its species that can be made about Compound 77427.

The second set of experiments described in JP10212235 (presented in Table 32) involves administration of Compound 44 to mice injected with *leukemia cell line* P388, and measurement of subsequent animal survival time. It is recognized in the art that leukemia does not form solid tumors. JP10212235 does not describe measuring any *in vivo* effect of administering Compound 44 other than increased subject survival time. JP10212235 does not describe *in vivo* measurement of cell proliferation, tumor size or angiogenesis. Nor is leukemia cell line P388 among those used in the *in vitro* assays (*see* Table 27, top section). No other compound was tested for *in vivo* effect. From this experiment, I conclude that Compound 44 has some anti-cancer effect, but without additional data, this effect cannot be defined. Additionally, because it is the only compound tested *in vivo*, and because the other experiment described in JP10212235 shows that species of Compound I have widely variable activities in the *in vitro* assay, it is not possible to infer any general properties of Compound I or its species from the *in vivo* data. Moreover, the GRP receptor has not been detected on leukemia cells. Thus, Compound 44's undefined anti-cancer effect cannot imply anything about any potential anti-GRP effect of Compound 44 or any other species of Compound I. (*Cuttitta Declaration*,¶¶7.2-7.4)

The Data in JP10212235 Does Not Imply or Predict the Activity of Compound 77427

Furthermore, the data presented in JP10212235 does not imply and would not allow one of skill in the art to predict anything about the biological activity of described Compound 105, which the Office alleges is identical to recited Compound 77427. Dr. Cuttitta notes that the structures of the compounds tested in JP10212235 are distinctly different from Compound 105, and describes the implications of this difference in chemical structure on activity as follows:

The Office equates Compound 105 and recited Compound 77427. Even though these compounds are the same, one of skill in the art could not infer any properties about Compound 105 from the *in vitro* or *in vivo* data presented in JP10212235. Compound 105 is not used in any of the described experiments, nor does the data presented in JP10212235 describe or suggest any specific efficacy of Compound 105 that would motivate one of skill to test it. One of skill in the art could not infer anything about the biological effects of Compound 105 from the presented data because the chemical structure of Compound 105 is quite different from the nine tested compounds. To illustrate these differences, submitted herewith as **Exhibit DD** is a comparison of the structures of the nine compounds used in the experiments with that of Compound 105. **Exhibit DD** provides the structural description of the nine particular species that were tested in experiments in JP10212235 (copied from Tables 1-26), as well as Compound 105 (which was not tested). As shown in **Exhibit DD**, it is clear that all of the compounds used in the *in vitro* and *in vivo* experiments have a cyclic, branched functional group at the position labeled R3 that is distinctly different from the non-cyclic,

> unbranched R3 group of Compound 105. It is also clear that all nine of the tested compounds share very similar R3 groups. Because of these structural differences between the nine similar tested compounds and Compound 105, one of skill in the art would not have been able to necessarily infer that Compound 105 would share any biological property with any of the other compounds presented in **Exhibit DD**.
>
> The September 2010 Declaration describes Compound 77427 as a small molecule mimetic of the GRP functional antagonist, monoclonal antibody 2A11 (*see* ¶8). Just as changes in an antibody's peptide structure may significantly affect its binding specificity, so too changes in chemical structure of a small molecule mimetic will affect its activity. As shown in **Exhibit DD**, the differences in structure between Compound 105 and the nine tested compounds are sufficiently significant that without experimental evidence, I do not believe one of skill would or could infer that Compound 105 shares the same biological properties as the other nine compounds. (*Cuttitta Declaration*, ¶¶7.5 and 7.6)

In view of Dr. Cuttitta's statements, Applicants submit that JP10212235 does not necessarily describe an anti-angiogenic effect of its "anti-tumor" compounds. Additionally, one of skill in the art would not and could not necessarily infer from JP10212235 that the "anti-tumor" compounds of JP10212235 have an anti-angiogenic effect. Moreover, the data presented in JP10212235 cannot be used to imply anything about the activity of recited Compound 77427. Thus JP10212235 cannot inherently anticipate the claimed methods of treating angiogenesis-mediated growth of a solid tumor.

JP10212235 does not inherently describe inhibiting an aberrant activity of GRP

The Office acknowledges that "JP 10212235 is silent as to the effect of the elected compound to inhibit an activity of a gastrin releasing peptide (GRP)" (Office action, at page 4). However, the Office continues to assert that "the administration of the claimed compound to patients suffering from cellular proliferative disorders is expected to necessarily have the claimed effect of inhibiting an activity of GRP" (*Id.*). In the interests of furthering prosecution, claim 80 has been amended to recite a method of "inhibiting an ***aberrant*** GRP activity."

As discussed above, to prove inherent anticipation, the Office must demonstrate that the asserted reference ***necessarily*** describes the claimed invention. As Dr. Cuttitta states, JP10212235 does not provide the necessary experimental evidence to support this assertion:

> The Office indicates that administration of a compound of generic formula (1) (hereinafter "Compound I") and its species to a subject as an "anti-tumor" therapy

necessarily implies inhibition of a GRP activity. Based on my training and experience, I do not think that it is possible to support this inference without experimental evidence. First, the Office's assertion pre-supposes that *all* cancer treatments function through the same mechanism. As discussed herein (*see* ¶6.2), one of skill in the art would be well aware that different cancer treatments may or may not have the same cellular target. Second, the Office's assertion assumes that all cancers are mediated by GRP. This is not the case. Any cell (including a cancer cell) must express the GRP receptor to be sensitive to GRP. Without the GRP receptor, a cell cannot and will not respond to GRP in the cellular environment. Thus, without the GRP receptor in a given cell, a GRP-specific inhibitor cannot and will not inhibit an activity in that cell.

One example of a cancer cell type that is insensitive to GRP is leukemia, which is known not to express the GRP receptor. Additionally, it is well-appreciated that the GRP receptor is not even universally expressed in all cell lines of those cancer types known to express the GRP receptor. This concept is illustrated by Moody *et al.* (*J. Cell. Biochem. Supp.*, 24:247-256, 1996; submitted herewith as **Exhibit AA**). Lung cells are known to express the GRP receptor. Moody *et al.* assay for the presence of the GRP receptor in several small cell lung cancer cell lines and several non-small cell lung cancer cell lines. Moody *et al.* demonstrate that the GRP receptor is present in many, but not all of the cell lines tested. Table I of Moody *et al.* shows that only 42% of small cell lung cancer and 32% of non-small cell cancer cell lines tested express the GRP receptor. Thus, the presence of the GRP receptor in a cancer type or cell line cannot be assumed without experimental verification or prior knowledge of its expression.

The claimed invention is directed to methods of inhibiting an aberrant GRP activity and methods of treating a condition that includes the step of "selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity." As discussed above, inhibiting a GRP activity requires that target cells express the GRP receptor. In contrast, JP10212235 does not require or suggest that the anti-tumor treatment based on Compound I inhibits an aberrant GRP activity. JP10212235 does not require that target cells express the GRP receptor. Nor does JP10212235 teach a step of selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity. JP10212235 describes an extensive list of cancer types that may be treated with Compound I and its species (¶35). However, this list includes cancer types, such as leukemia, that are known not to express the GRP receptor. Moreover, in view of Moody et al., one of skill would have appreciated at the time of Applicants' priority date that even those cancer types known to express the GRP receptor will have derivative cell lines or disease strains that do not. Thus, without specifying that the treatment is inhibiting an aberrant GRP activity or indicating particular cell lines known to express the GRP receptor, JP10212235 does not necessarily describe inhibition of an aberrant GRP activity. Nor would one of skill infer that JP10212235 describes inhibition of an aberrant GRP activity. (*Cuttitta Declaration*, ¶¶5.1-5.3)

Thus, JP10212235 must indicate that the tumors being treated necessarily express the GRP receptor in order to anticipate the claimed methods of inhibiting an aberrant GRP activity,

either *in vitro* or *in vivo*. Applicants submit that JP10212235 contains no such teachings and does not anticipate the claimed methods of inhibiting an aberrant GRP activity.

In view of the foregoing amendments and arguments, Applicants respectfully request withdrawal of the rejection of claims 80, 81, 90, 94-97 and 100-103 under 35 U.S.C. §102(b).

JP10212235 does not anticipate new claims 104-108

New claim 104 is directed to inhibiting a GRP activity *in vitro*. New claims 105-108 include the steps of detecting or monitoring inhibition of angiogenesis (claims 105 and 107) or inhibition of tumor growth (claims 106 and 108). As discussed above, JP10212235 does not describe *in vitro* inhibition of GRP, nor does it describe *in vivo* detection of angiogenesis or inhibition of tumor growth. Accordingly, Applicants submit that new claims 104-108 are not anticipated.

Rejoinder of Withdrawn Claims

Applicants submit that based on the foregoing arguments, generic claims 80 and 90 are in condition for allowance. Applicants request that claims 91-93 be rejoined, examined, and allowed at this time.

CONCLUSION

Based on the foregoing amendments and arguments, the pending claims are in condition for allowance, and notification to that effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Michael D. Hammer/
Michael D. Hammer, Ph.D.
Registration No. 59,258